in the Amendment filed October 10, 2000 (*see*, page 2 of the Office Action mailed January 11, 2001).

In the present Office Action, the rejection of claims 1-28 under 35 U.S.C. § 112, first paragraph, has been maintained. In addition, claims 1-28 have been newly rejected under 35 U.S.C. § 112, first paragraph. Each of these rejections is addressed in turn below.

Maintained Rejection Under 35 U.S.C. § 112, First Paragraph

The Office Action maintains the rejection of claims 1-28 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. In the Office Action, the Examiner has indicated that enablement is provided for the treatment of neoplasia comprising tumor reduction and tumor treatment in various appropriate animal models (*see*, page 3 of the Office Action). More particularly, the Examiner has indicated that treatment comprising the systemic administration of recombinant "hyper" type 1 thymidine kinase, which recombinant nucleic acid is encapsulated in the lipid formulation denoted as either Formulation 1.1 or 1.2 (*see*, pages 23-24 of the specification), and which treatment further comprises the administration of ganciclovir also encapsulated in the lipid formulations denoted as either Formulation 1.1 or 1.2 is enabled by the specification as originally filed (*see*, page 3 of the Office Action). However, the Office Action alleges that the specification does not provide enablement for the treatment of all possible neoplasms in mammals comprising the administration of any and/or all serum stable nucleic acid-lipid particles comprising any and/or all nucleic acids (*see*, page 3 of the Office Action). Applicants respectfully ***disagree*** and traverse this ground of rejection.

As previously explained, a particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention ***without*** undue experimentation. *See, e.g., In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988), or MPEP §2164.01. It is important to note that the possibility that some experimentation, even if such experimentation is complex or extensive, may be required for the practice of the invention does not necessarily mean that the invention is not enabled:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See*, MPEP § 2164.01.
>
> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the

> specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. MPEP § 2164.06, citing *In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988).

In the present case, the Office Action provides no objective, scientific evidence as to why the claims are enabled for a number of embodiments, but not for others. For instance, why are the claims enabled for Formulations 1.1 and 1.2 and not Formulations 1.3, 1.4 and 1.5. A review of these lipid formulations reveals that Formulations 1.1 through 1.4 primarily differ from one another in terms of the mole percents of DOPE, DODAC and PEG-Cer present in the lipid formulations, and Formulation 1.5 primarily differs from Formulations 1.1 through 1.4 in that it contains DSPC and not DOPE and in that it further comprises cholesterol. In addition, no objective, scientific evidence is provided as to why the claims are enabled for particular nucleic acid, but not for others. Instead of providing objective, scientific reasons why the claims are not fully enabled, the Office Action generally refers back to the previous Office Action mailed April 10, 2000 (*see*, page 3 of the Office Action). However, none of the potential issues raised by the Examiner in the Office Action mailed April 10, 2000 establish (1) a scientific basis as to why the claims are enabled for a number of embodiments, but not for others; or (2) a scientific basis as to why one of skill would have been required to undertake an "undue" amount of experimentation in order to practice the scope of the claimed invention.

A perusal of the present specification reveals that it provides extensive guidance, including working examples, for practicing the claimed invention. For instance, the specification provides the following:

- teachings regarding therapeutic nucleic acids (*see*, *e.g.*, page 10, line 14 to page 14, line 24);
- teachings regarding the preparation and properties of the lipid/therapeutic nucleic acid particles (*see*, *e.g.*, page 14, line 25 to page 18, line 31);
- teachings regarding the disease indications suitable for treatment using the lipid-nucleic acid particles of the present invention (*see*, *e.g.*, page 19, line 28, to page 20, line 16);

- teachings regarding combination therapies that can be used with the lipid-nucleic acid particles of the present invention (*see, e.g.*, page 20, line 17, to page 21, line 21);
- teachings regarding administration-ready pharmaceutical preparations (*see, e.g.*, page 19, line 1, to page 19, line 27); and
- teachings regarding the administration of the lipid-nucleic acid particles (*see, e.g.*, page 21, line 20, to page 22, line 27).

Further, the specification provides numerous examples describing, *e.g.*, the preparation of lipid-plasmid particles (Examples 1 and 4), the delivery of lipid-formulated ganciclovir to mice having tumor cells transfected with HSV-TK (Examples 2, 3, 4A, and 11), the delivery and detection of nucleic acids to tumor cells *in vivo* (Examples 6, 11, 13, 14 and 15), the delivery of lipid-formulated TK-encoding plasmids and ganciclovir to mice harboring tumor cells (Example 7), and the preparation, pharmacokinetics, and biodistribution of lipid-formulated ganciclovir (Examples 8, 9 and 10). It is noted that many of these examples are working examples performed in model animals, providing clear evidence of the enablement of the claimed methods as required by the case law (*see, In re Jolles*, 206 USPQ 885 (CCPA 1980)).

Taken together, such examples ***unequivocally establish*** that the lipid-nucleic acid particles of the present invention ***are capable of transforming cells and effecting phenotypic changes*** such as reduction in tumor proliferation and size. In fact, as mentioned above, the Examiner has indicated in the Office Action that enablement is provided for the treatment of neoplasia comprising tumor reduction and tumor treatment in various appropriate animal models (*see*, page 3 of the Office Action). Again, however, the Office Action provides no objective, scientific basis for the allegation that the claims are enabled for some embodiments, but not for others. Clearly, the extensive guidance provided in the specification, and the presence of numerous working examples in animal models, are more than sufficient to establish the enablement of ***all*** of the claims currently under examination, *i.e.*, claims 1-28.

In the Office Action mailed April 10, 2000, the Examiner cited a number of references that allegedly demonstrate that gene therapy is unpredictable and surrounded by significant hurdles. However, as explained in Applicants' Amendment filed October 10, 2000, a perusal of the cited references reveals that contrary to the Examiner's allegation, such references

support the proposition that gene therapy works. Thus, these references (*i.e.*, Crystal *et al.*, Varma *et al.*, Friedman and Schofield *et al.*) coupled with Applicants' examples showing the ability of the lipid-nucleic acid particles of the present invention to deliver genes and drugs to distal tumor cells and to reduce or prevent tumor grow ***clearly demonstrate*** that gene therapy works. Again, Applicants examples ***unequivocally establish*** that the lipid-nucleic acid particles of the present invention are capable of transforming cells and effecting phenotypic changes such as reduction in tumor proliferation and size.

In view of all of the above, Applicants assert that claims 1-28 are fully enabled by the specification as originally filed. Accordingly, Applicants respectfully request that the rejection under § 112, first paragraph, be withdrawn.

New Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-28 have been newly rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (*see*, page 4 of the Office Action). In making this rejection, the Office Action alleges that the specification does not describe elements which are essential to various functions of the claimed invention. For instance, the Office Action alleges that the specification does not describe elements that are essential to the definition of the term "gene" (*see*, page 4 of the Office Action). In addition, the Office Action alleges that the specification does not describe elements essential to the lipid-nucleic acid particles of the present invention (*see*, page 4 of the Office Action). Moreover, the Office Action alleges that concise structural features that could distinguish structures or compounds within a genus from others are missing from the specification (*see*, page 5 of the Office Action). Applicants respectfully ***disagree*** and traverse this ground of rejection.

The present invention provides, *inter alia*, methods and compositions for treating a neoplasia, *e.g.*, a tumor, in a mammal. For instance, in one embodiment, the present invention provides a method of treating a neoplasia in a mammal, the method comprising administering to the mammal a serum-stable nucleic acid-lipid particle comprising a nucleic acid that is fully encapsulated within a lipid, wherein the administration is by injection at an injection site that is distal to the neoplasia in the mammal.

As such, the methods of the present invention involve the use of a compound, *i.e.*, a nucleic acid-lipid particle, comprising: (1) a nucleic acid and (2) a lipid, and wherein the nucleic acid is fully encapsulated by the lipid. A perusal of the specification reveals that more than sufficient guidance is provided regarding the meaning of the term "nucleic acid," and numerous examples of nucleic acids suitable for use in the present invention are provided (*see, e.g.*, page 10, line 14 to page 14, line 24). In addition, the specification provides more than sufficient guidance regarding the term "lipid," and numerous examples of lipids suitable for use in preparing the nucleic acid-lipid particles of the present invention are provided (*see, e.g.*, page 14, line 25 to page 18, line 31). Moreover, the specification provides more than sufficient guidance regarding methods for preparing the nucleic acid-lipid particles of the present invention, wherein the nucleic acid is fully encapsulated by the lipid (*see, e.g.*, page 14, line 25 to page 18, line 31). In fact, the examples provide assays for determining the serum stability and nuclease resistance of the nucleic acid-lipid particles of the present invention (*see, e.g.*, page 30, line 6 to page 31, line 6). Thus, contrary to the allegations set forth in the Office Action, the specification and claims do, in fact, provide the concise structural features/elements of the compounds, *i.e.*, the nucleic acid-lipid particles, used in the methods of the present invention.

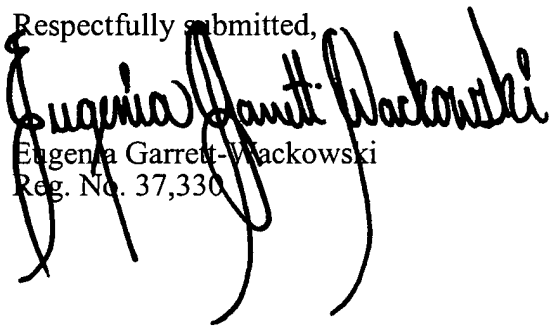
In view of the foregoing, Applicants respectfully submit that the claims recite subject matter that was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As such, Applicants urge the Examiner to withdraw this rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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